Ventilator-induced brain injury: another iatrogenic complication of mechanical ventilation

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Purpose of review
Mechanical ventilation is life-saving, but is increasingly recognized to be involved in adverse neurological outcomes. Ventilator-associated brain injury (VABI) refers to primary brain dysfunction directly attributable to mechanical ventilation, independent of sedation, hypoxemia, or sepsis. This review summarizes current evidence on the pathophysiology, clinical impact, monitoring strategies, and potential therapeutic interventions for VABI.

Recent findings
A growing number of preclinical and clinical studies suggest that mechanical ventilation contributes to hippocampal apoptosis, maladaptive vagal and purinergic signaling, neuroinflammation, blood–brain barrier disruption, altered CO_2 regulation, and nasal airflow abolition. Clinically, VABI may manifest as delirium, disordered sleep, prolonged weaning, and long-term cognitive impairment. Monitoring tools such as electroencephalography, near-infrared spectroscopy, cerebral biomarkers, Doppler ultrasound, and MRI offer complementary but indirect insights. As of today, preventive and therapeutic strategies focus on lung-protective ventilation, limited sedation, early mobilization, and good quality sleep promotion. Some innovative approaches such restoration of nasal airflow, phrenic and vagal stimulation remain experimental.

Summary
VABI is increasingly recognized as a critical research frontier in critical care medicine. Awareness of its mechanisms and clinical impact should prompt ICU clinicians to integrate brain-oriented practices into routine care. Future trials are needed to evaluate preventive strategies and improve long-term cognitive and functional outcomes for ICU survivors.

Keywords
cognitive dysfunction, critical care, mechanical ventilation, neurologic deficits

INTRODUCTION

Mechanical ventilation is a life-saving treatment supporting critically ill patients. Historically, concerns about brain dysfunction during mechanical ventilation were largely confined to patients with acute brain injury, where ventilatory strategies can increase intracranial pressure, reduce cerebral perfusion, and impair brain tissue oxygen metabolism [1]. Respiratory management is recognized as a determinant of neurological outcomes in patients admitted to the ICU with brain injury, with practices such as positive end-expiratory pressure (PEEP) directly affecting cerebral physiology [1]. While ventilation practices in brain-injured patients clearly influence outcomes, emerging evidence suggests that mechanical ventilation itself may contribute to brain dysfunction in critically ill patients without preexisting neurological injury, a phenomenon termed as ventilator-associated brain injury (VABI) by a group of authors [2▪▪]. Critically ill patients often carry multiple risk factors that may contribute to VABI [3], including inappropriate ventilatory settings, hypoxemia, systemic inflammation, and relevant

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KEY POINTS

- Mechanical ventilation can directly contribute to brain injury or dysfunction, a phenomenon termed ventilator-associated brain injury (VABI).
- Pathophysiological mechanisms include vagal and purinergic signaling, neuroinflammation, blood–brain barrier disruption, altered CO_2 regulation, and loss of nasal airflow.
- Clinically, VABI manifests as delirium, sleep disruption, dyspnea, prolonged weaning, and long-term cognitive impairment, contributing to postintensive care syndrome.
- Monitoring strategies, such as EEG, NIRS, ultrasound, MRI, and biomarkers, can complement bedside neurological assessment, though integration remains essential.
- Bundled approaches that combine light sedation, protective ventilation, dyspnea relief, early mobilization, and sleep promotion offer the best current protection against VABI.

comorbidities [2▪▪]. As for the demonstration of ventilator induced diaphragm dysfunction, one of the key challenges lying in VABI is to isolate the respective influence of mechanical ventilation on the brain, in particular in the ICU setting. Parallel to these findings, clinical data confirm that survivors of critical illness without primary brain injury often experience long-term cognitive impairment [4], with systematic reviews supporting an association between mechanical ventilation exposure and neurocognitive dysfunction [2▪▪]. In this context, the present review synthesizes preclinical and clinical evidence on VABI, its underlying mechanisms, clinical implications and potential therapeutic pathways.

TOWARD A CONCEPTUAL DEFINITION OF VENTILATOR-INDUCED BRAIN INJURY

The concept of VABI was formally introduced as a research priority by Bassi *et al.* [2▪▪], as a de-novo brain injury or dysfunction directly attributable to positive pressure mechanical ventilation, independent of co-interventions or confounding factors. Preclinical studies have been pivotal in establishing the concept of VABI, suggesting that mechanical ventilation can directly trigger neuronal injury and provide biological plausibility for brain dysfunction arising from mechanical ventilation [2▪▪,5,6]. Clinical observations reinforce this link, as cognitive impairment and long-term neuropsychological deficits are frequently reported in ICU survivors without primary neurological disease, with systematic reviews indicating a contribution of mechanical ventilation exposure to this burden [3,4]. Therefore, experimental and clinical evidence support VABI as a distinct clinical and research concept, extending concern from patients with brain injury to the broader population of critically ill patients receiving mechanical ventilation. However, it remains challenging to specifically isolate the influence of mechanical ventilation on long term neurological outcomes, and further studies are needed. See Fig. 1 for an overview of the risk factors and clinical manifestation of VABI (Fig. 2).

PATHOPHYSIOLOGICAL MECHANISMS

The interaction between the respiratory system and the brain is bidirectional [2▪▪]. Acute brain injury may trigger pulmonary complications, while lung injury, including ventilator-induced lung injury, can disrupt cerebral homeostasis [2▪▪]. Mechanical ventilation can amplify this brain-lung interaction by triggering systemic inflammation, altering vagal signaling, and impairing blood–brain barrier integrity, ultimately leading to neuronal injury [3,4]. Beyond these mechanisms related to mechanical ventilation, common co-exposures such as sedation, analgesics, neuromuscular blockers, immobilization, and sleep disruption, further contribute to VABI and clinically may manifest as delirium, long-term cognitive impairment, and hindered neural recovery [4]. These co-exposures complicate disentangling the direct effects of mechanical ventilation and underscore the need to examine the specific pathophysiological mechanisms by which mechanical ventilation affects the brain.

Pulmonary stretch and neural signaling

MV induced-lung inflation stretches the lung, stimulating vagal afferents. This influences brainstem and cortical activity [2▪▪]. The Hering–Breuer reflex, a vagally mediated feedback mechanism, normally protects against overinflation and regulated respiratory muscle activity as a protective mechanism [7]. Under mechanical ventilation and sedation however, this physiological feedback may be blunted, and excessive or abnormal stretch can induce maladaptive signaling, resulting in hippocampal dopamine imbalance and neuronal apoptosis [7]. Mechanosensory pathways, such as transient receptor potential vanilloid 4 (TRPV4) channels, may propagate this effect through purinergic receptor activation and subsequent hippocampal inflammation [5]. This cascade promotes dopamine release in the hippocampus, triggers neuroinflammation, and resulting in cell death [5]. Autopsy studies confirm

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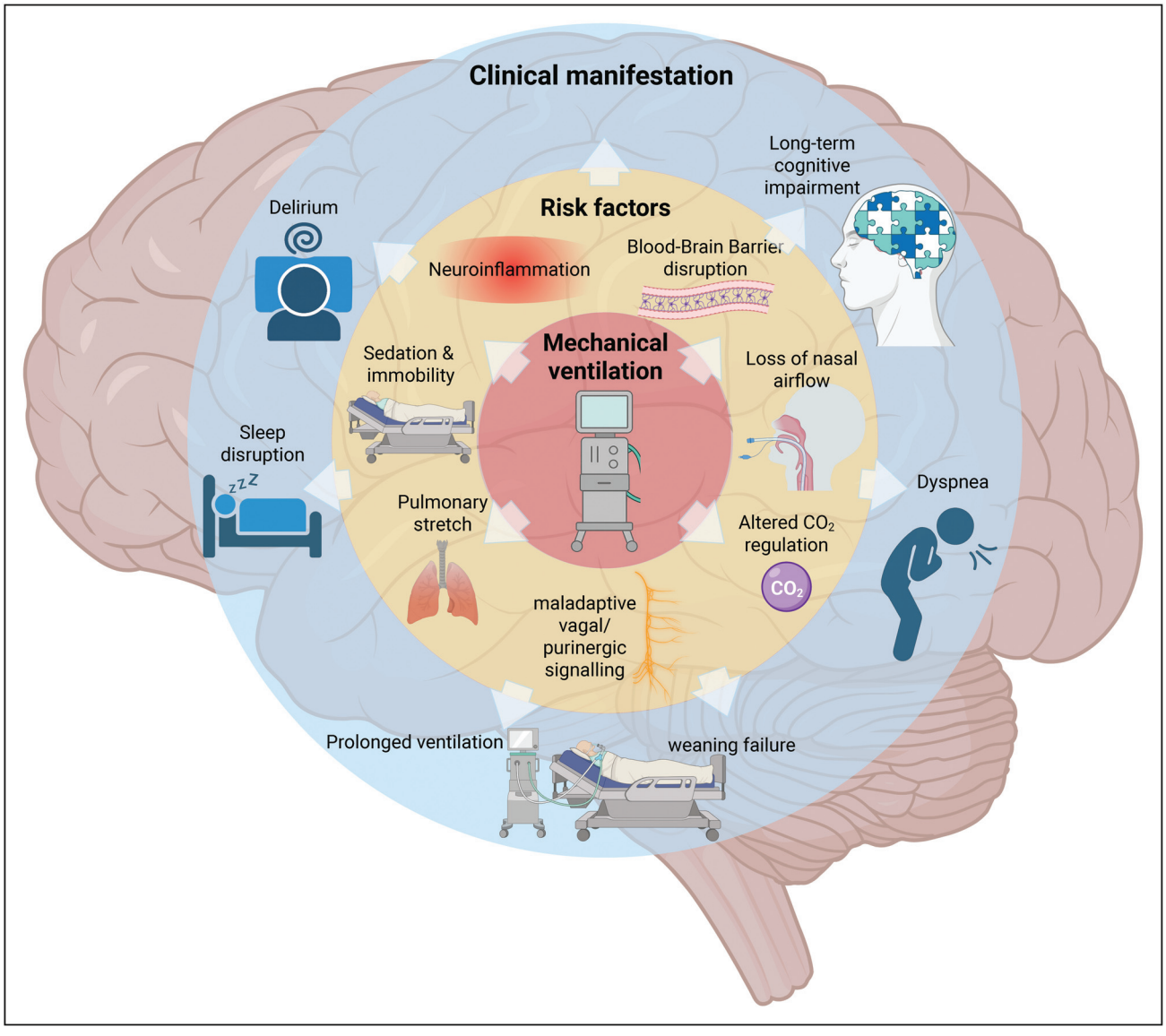

FIGURE 1. Conceptual framework of ventilator-associated brain injury. Mechanical ventilation (MV) may directly contribute to brain dysfunction through multiple interrelated mechanisms. Together, they create a vicious cycle that complicates liberation from MV and increases the risk of persistent neurocognitive sequelae in ICU survivors.

altered TRPV4 expression in ventilated patients, suggesting clinical relevance [5]. Disruption of this normal physiological signaling, by sedation or excessive stretch through mechanical ventilation, can further dysregulate autonomic tone, contributing to neurocognitive impairments [2▪▪].

Neuroinflammation-mediated neuronal injury

Mechanical ventilation rapidly induces systemic and cerebral inflammation [3], with animal studies showing increased hippocampal and systemic expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α within only 6 h of mechanical ventilation [3]. This inflammatory cascade activates microglia and astrocytes, upregulates Toll-like receptor pathways, and initiates apoptosis through caspase and mitochondrial mechanisms. Such processes interfere with long-term potentiation, a neural correlate of memory, providing a mechanistic link to cognitive impairment [3]. In parallel, systemic inflammation and cyclic mechanical stress can disrupt blood-brain barrier integrity, permitting cytokines and other neurotoxic mediators to enter the central nervous system [2▪▪]. Together, these processes amplify acute neuronal injury during mechanical ventilation and may underlie the persistent cognitive impairment observed in ICU survivors [4].

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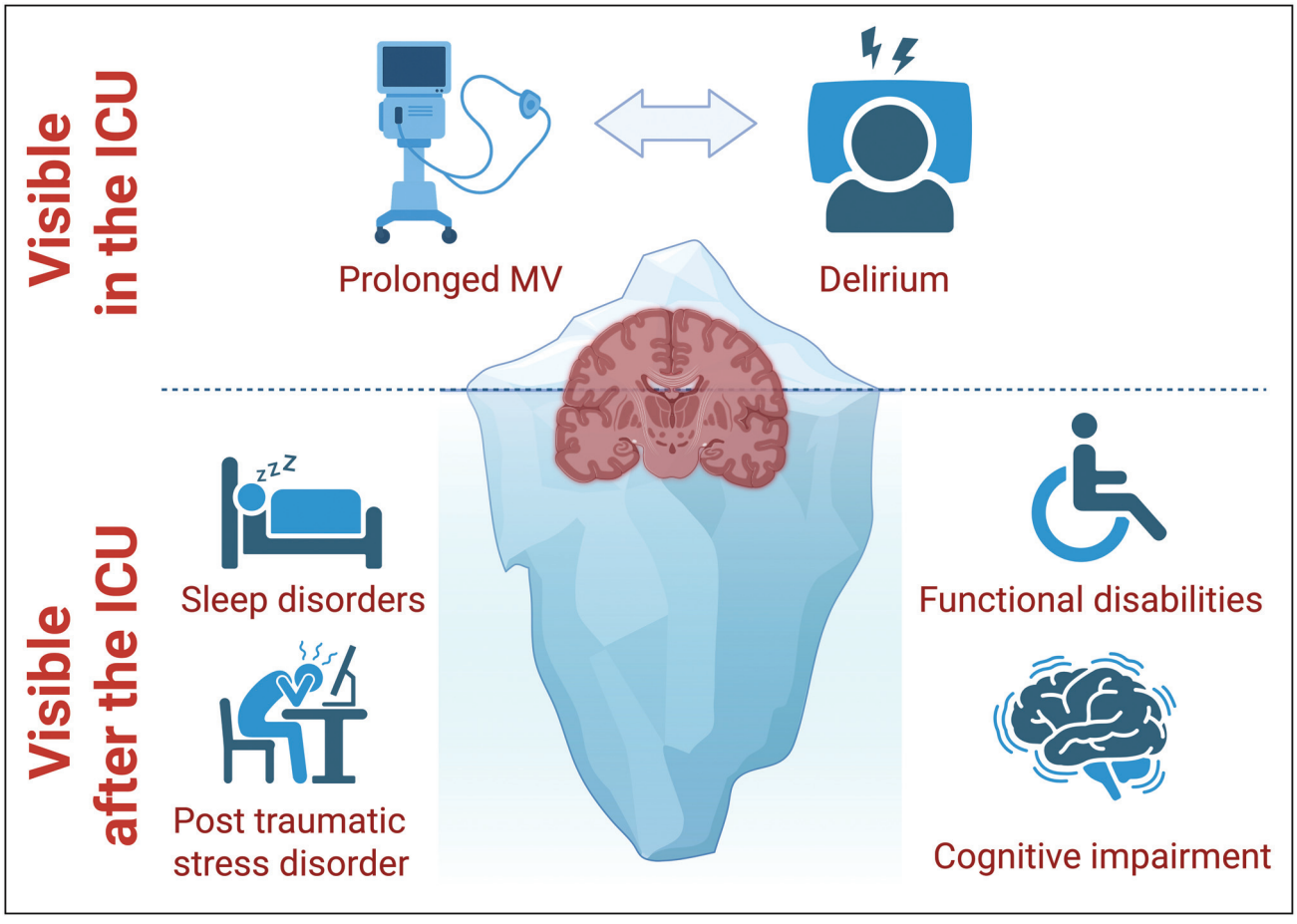

FIGURE 2. Visible manifestations of ventilator-associated brain injury in the ICU and after the ICU.

Brain and respiratory signals coupling

In mammals, airflow through the nasal cavities generates rhythmic oscillations transmitted by the olfactory bulb and nasal airway receptors to limbic and cortical structures, thereby modulating brain activity in regions involved in memory and cognition [8]. Cognitive performance is enhanced during nasal compared with oral breathing, supporting the concept of a link between nasal airflow and higher brain function [8]. Consequently, the abolition of nasal stimulation, intrinsic to endotracheal intubation and tracheostomy, may contribute to cognitive impairment in mechanical ventilation patients, particularly during prolonged mechanical ventilation when this disruption may amplify other VABI risk factors [9]. Experimental studies demonstrate that nasal airflow loss impairs hippocampal function [9], whereas restoration with nasal air puffs during invasive ventilation enhances electroencephalographic activity and connectivity [9]. Translational observations in comatose patients support these findings [10▪▪], and recent data show that nasal high flow reduces dyspnea and respiratory drive in orally intubated patients [10▪▪]. These results provide a biological foundation for exploring nasal stimulation as an innovative intervention to mitigate delirium and potentially shorten the duration of mechanical ventilation [3].

Carbon dioxide and cerebral blood flow

Carbon dioxide (CO_2) is a potent regulator of cerebral perfusion. Hypercapnia induces vasodilation and increases cerebral blood flow, whereas hypocapnia causes vasoconstriction and reduces flow, potentially compromising oxygen delivery [11]. Experimental and clinical studies confirm that cerebrovascular CO_2 reactivity is preserved in mechanical ventilation patients [12]. As a result, common ICU practices, such as permissive hypercapnia, extracorporeal CO_2 removal, or hyperventilation, may inadvertently influence cerebral hemodynamics thus impairs neurological outcomes [11].

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CLINICAL MANIFESTATION OF VENTILATOR-INDUCED BRAIN INJURY

Delirium and cognitive impairment

Delirium is common in mechanical ventilation patients and remains a strong predictor of poor outcomes. Its pathogenesis is multifactorial, with mechanical ventilation related contributors including vagal afferent disruption, altered cerebral perfusion, inflammation, and sedative exposure [2▪▪]. Each additional day of delirium is independently associated with worse long-term cognition as demonstrated in a large prospective cohort [2▪▪]. At 3 and 12 months after hospital discharge, survivors often show cognitive deficits comparable to those seen in mild Alzheimer disease or moderate traumatic brain injury [2▪▪]. Meta-analyses confirm that cognitive impairment is a major component of postintensive care syndrome, affecting quality of life, ability to cope with daily activities, and return to work [4].

The consequences of VABI extend well past hospitalization. Cognitive impairment after critical illness is strongly associated with reduced health-related quality of life, functional dependence in daily activities, delayed or absent return to work, and increased caregiver burden [4]. These sequelae often persist for years, making VABI a central contributor to the long-term disability burden of ICU survivors.

Sleep disruption

Mechanical ventilation is a risk factor for sleep disturbances in the ICU [13]. Sleep is typically fragmented, with loss of slow-wave and rapid eye movement (REM) phases, and sedatives fail to restore normal sleep architecture [13]. Abnormal sleep has been linked to delirium, impaired ventilatory control, and long-term cognitive decline [4]. Persistent sleep disruption has downstream consequences, contributing to post intensive care syndrome and being associated with physical disability, mental health disorders, and reduced health-related quality of life up to a year after ICU discharge [13].

Prolonged mechanical ventilation

Prolonged mechanical ventilation is itself an independent risk factor for brain injury. Preclinical studies demonstrate persistent neuroinflammation and hippocampal apoptosis [3,4]. Clinically, patients requiring long-term ventilation often develop neuromuscular weakness, impaired respiratory drive, and cognitive disturbances that hinder liberation from the ventilator [14]. In intubated or tracheostomized patients, bypassing the nasal airway further disrupts physiological respiratory-brain signaling, a mechanism that may aggravate VABI, particularly when combined with sedation, delirium, and sleep fragmentation [10▪▪]. Emerging evidence indicates that mitigating the loss of nasal airflow, especially during prolonged weaning, could support both ventilator liberation and cognitive recovery.

Dyspnea

Dyspnea is a frequent but under-recognized symptom during weaning, reflecting load–capacity imbalance and increased respiratory drive [10▪▪]. Beyond its respiratory implications, dyspnea engages cortical and limbic brain activity, and when sustained, may contribute to neuro-affective stress and memory disturbances relevant to VABI [15]. Clinically, dyspnea is associated with weaning failure and post-ICU psychological distress, including anxiety and posttraumatic stress [16]. Repeated failed spontaneous breathing trials, although not caused by dyspnea alone, may prolong ICU stay and worsen functional recovery [16]. These observations support systematic assessment of dyspnea and neurocognitive symptoms during weaning, alongside conventional cardiopulmonary monitoring.

MONITORING OF VENTILATOR-ASSOCIATED BRAIN INJURY

Bedside neurological functional assessments, such as the Confusion Assessment Method for the ICU (CAM-ICU) for delirium [17] and the Richmond Agitation Sedation Scale (RASS) for sedation [18], are central for detecting brain abnormal activity in ventilated patients, but in practice, there are often limited by sedation, delirium, and neuromuscular blocking agents. Objective monitoring techniques can complement clinical evaluation, support early detection of VABI, and guide treatment or prognostication. Available tools include electroencephalography (EEG), near-infrared spectroscopy (NIRS), ultrasound-based assessments, MRI, and biomarkers.

Electroencephalography

EEG provides continuous assessment of cortical electrical activity and remains the gold standard for detecting nonconvulsive seizures and status epilepticus [19]. Continuous EEG is superior to intermittent recordings, with up to one-third of critically ill patients showing seizures, even without clinical correlates [19]. Beyond seizure detection, EEG patterns can reflect sedation depth, delirium, cognitive impairment, and evolving encephalopathy [19]. In sepsis-associated encephalopathy, slowing of background rhythms, triphasic waves, and loss of reactivity are

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associated with poor outcomes [19]. Advanced post-processing, including connectivity analyses, shows that respiratory cycles and critical illness can alter large-scale brain coordination, though clinical use remains exploratory [8]. However, sedatives and hypothermia complicate interpretation, and EEG findings should be integrated with other modalities.

Near-infrared spectroscopy

NIRS is a noninvasive method to estimate regional cerebral oxygen saturation. NIRS is often used in operating rooms as a surrogate marker of cerebral perfusion. During surgery, low cerebral oxygen saturation is associated with delirium and long-term cognitive decline, prompting interest in its use in the ICU [20]. A systematic review of NIRS in critically ill patients found that low regional cerebral oxygen saturation values were consistently associated with delirium, though statistical significance was achieved in only half of the studies [21]. Coupled with blood pressure monitoring, NIRS may help define cerebrovascular autoregulation indices and guide individualized hemodynamic targets [21]. These indices may help individualize blood pressure targets and optimize cerebral perfusion during ventilation [21]. Yet, limitations, such as extracranial signal contamination and heterogeneity in methodologies used in literature restricts its implementation in routine ICU care [21].

Doppler ultrasound assessments

Bedside brain ultrasound provides a practical, noninvasive, repeatable option for assessing cerebral hemodynamics. Transcranial Doppler (TCD) allows real-time measurement of cerebral blood flow velocities and autoregulation indices, such as the mean flow index (Mx) and the pressure reactivity index (PRx) [22]. Abnormal values are common in septic and ventilated patients and have been linked to delirium and encephalopathy [22]. TCD can also evaluate responses to interventions such as fluid resuscitation, vasoactive agents, or ventilatory maneuvers [22]. Optic nerve sheath diameter (ONSD) offers an estimate of intracranial pressure, though predictive accuracy for VABI remains inconsistent [22]. Evidence overall is heterogeneous, and integration with other modalities is essential [22].

MRI

MRI offers detailed structural information on brain injury but its use limited by feasibility in unstable mechanical ventilation patients. When performed, common findings include small ischemic lesions, microhemorrhages, diffuse white matter changes, and posterior reversible encephalopathy syndrome [23]. Advanced methods such as arterial spin labeling suggest altered cerebral blood flow in delirium, but findings remain inconsistent [21]. Given these constraints, MRI is typically reserved for unexplained or persistent encephalopathy after exclusion of metabolic and systemic causes [23].

Biomarkers

Plasmatic biochemical markers of brain injury may provide complementary insights [24]. The most promising biomarkers are central nervous system-derived proteins, including S100 calcium-binding protein beta (S100β), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NfL) which reflect astrocytic and neuronal injury and have been associated with delirium, coma, and long-term cognitive impairment [23,24,25▪▪]. Inflammatory markers such as interleukin-6, TNF-α, and CRP may reflect mechanisms contributing to VABI, including blood–brain barrier permeability and microglial activation, but their specificity remains low [24]. Interpretation is further complicated by extracerebral sources, renal clearance, and systemic inflammation. At present, biomarkers are best considered exploratory tools to be combined with neuroimaging or electrophysiology [24].

Integration and multimodal monitoring

No single tool captures the multifactorial nature of VABI. Increasingly, a multimodal approach is advocated, combining EEG, perfusion monitoring (NIRS or TCD), surrogate ICP measures, and biomarkers [26]. Emerging artificial intelligence–based analyses of multimodal data may allow earlier detection of neurological deterioration and more individualized management [26]. For now, bedside feasibility, staff expertise, and integration into ICU workflows remain key determinants of clinical adoption.

PROTECTIVE AND TREATMENT STRATEGIES FOR VENTILATOR-ASSOCIATED BRAIN INJURY

As of today, preventing and treating VABI requires integrating sedation practices, ventilator management, nonpharmacologic strategies, and bundled care. While evidence is still evolving, several approaches are supported by both preclinical and clinical data. Bundled approaches such as the ABCDE/ABCDEF framework consistently improve outcomes without increasing nursing workload and may reduce long-term cognitive impairment [27].

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Sedation and awakening practices

Minimizing deep sedation and implementing paired spontaneous awakening and breathing trials reduce ventilation duration, sedative exposure, and delirium incidence [27]. Recommended strategies include using analgesia-first and nonbenzodiazepine sedation, daily interruption or titration to the lightest effective level, and EEG-informed adjustments when clinically indicated (e.g., refractory agitation, unexplained encephalopathy) [19].

Ventilation settings and gas exchange

Ventilator settings may influence brain injury. High tidal volumes, elevated driving pressures, and prolonged exposure exacerbate systemic inflammation, neuroinflammation, and neuronal apoptosis [5]. Even higher levels of PEEP, while often lung-protective, have been associated with abnormal neuronal activation [28]. Conversely, lung-protective ventilation, using lower tidal volumes (~6 ml/kg predicted body weight), adequate but not excessive PEEP, and avoiding hyperoxia or hypocapnia, attenuates adverse brain effects in experimental models [3,28]. Clinical data show that after out-of-hospital cardiac arrest, lower tidal volumes are associated with improved neurocognitive outcomes and more ventilator-free days, emphasizing the potential of lung-protective ventilation to mitigate brain injury [29].

Gas exchange targets are critical. Both hypercapnia and hypocapnia alter cerebral blood flow [11]. Hypocapnia from hyperventilation can reduce cerebral perfusion, while permissive hypercapnia or extracorporeal CO_2 removal ($ECCO_2R$) may have unintended cerebral consequences [11]. Ventilatory modes and assist levels can further influence patient–ventilator interaction and sleep: inappropriate support worsens fragmentation and asynchrony, while optimized modes may improve sleep quality [13].

Restoration of nasal airflow

Nasal breathing supports cortical and limbic oscillatory activity and may enhance cognitive performance [10▪▪]. Endotracheal and tracheostomy tubes bypass this pathway, potentially leading to or exacerbating VABI [5,9]. Preclinical studies show that restoring or mimicking nasal airflow reduces hippocampal inflammation and memory impairment [9]. Recent clinical data suggests that nasal high-flow therapy may relieve dyspnea in intubated or tracheostomized patients, supporting weaning and potentially improving neurocognitive recovery [10▪▪]. Strategies to reintroduce nasal airflow are low-burden and warrant further investigation as adjuncts to ICU care [9,10▪▪].

Early mobilization and cognitive stimulation

Physical rehabilitation and cognitive engagement during ICU stay may counteract immobility-related inflammation and reduce delirium duration [30]. have been associated with shorter delirium episodes and reduced ICU length of stay, though trial evidence remains heterogeneous and of low–moderate quality [30].

Diaphragm and vagal neurostimulation

Preserving diaphragm activity during mechanical ventilation may have neuroprotective effects. Preclinical studies demonstrate that transvenous phrenic nerve stimulation, to stimulate the diaphragm activation, applied early and maintained during lung-protective ventilation, mitigates hippocampal apoptosis, inflammation and cognitive impairment in animal models [6]. These effects are likely most relevant in patients requiring prolonged mechanical ventilation, who are vulnerable to diaphragm inactivity and VABI [1]. Vagal stimulation has also been proposed to modulate lung–brain inflammatory signaling and hippocampal injury, though this remains experimental and the optimal timing and clinical application remains undefined [5].

Multicomponent care

Integrated care bundles remain the most effective clinical approach. Strategies that combine light or no sedation, daily readiness assessments for spontaneous awakening and breathing trials, early progressive mobility, and sleep-promotion measures are consistently associated with shorter ventilation, fewer delirium days, and improved discharge outcomes [27].

CONCLUSION

Preclinical and clinical studies have established VABI as a distinct concept, with biological plausibility supported by pathways linking pulmonary stretch, vagal and purinergic signaling, systemic inflammation, blood–brain barrier dysfunction, altered CO_2 regulation, and loss of nasal airflow to structural and functional brain injury. Clinically, these mechanisms manifest as delirium, disordered sleep, dyspnea, prolonged weaning, and long-term cognitive impairment, central features of postintensive care syndrome that burden patients, families, and healthcare systems long after ICU discharge. At the bedside, preventive and therapeutic strategies already exist. Light or no sedation, paired awakening and breathing trials, lung-protective ventilation, early mobilization, and sleep-promotion measures all reduce risk factors associated with VABI and improve outcomes.

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Emerging avenues, including restoration of nasal airflow, diaphragm-preserving ventilation, and phrenic nerve stimulation, warrant further exploration. Bundled approaches that integrate sedation, ventilation, mobility, and sleep strategies appear most promising.

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Conflicts of interest

There are no conflicts of interest.

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